



# Regulatory Education for Industry (REdI): **GENERIC DRUGS FORUM**

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## **Update on Question-based Review (QbR)**

**Robert Iser**

Senior Scientific Advisor (acting)

Office of Process & Facilities / OPQ / CDER



# Presentation Objectives

- **Update on current QbR activities**
- **Future of QbR & regulatory submissions**
- **MaPP 5015.10**
- **FAQs on QbR & MaPP 5015.10**
- **Resources & References**

**How Many Have Submitted A  
QbR Submission?**



# QbR Background

- **Developed to assess generic drug applications as due to objectives of cGMP's for the 21st Century initiative**
- **Developed using lessons learned from other CDER and other regulatory authorities:**
  - **CDER MAPP 4000.4 (*Clinical Pharmacology and Biopharmaceutics Review Template*)**
  - **Health Canada**
- **Use the quality overall summary as a foundation for the primary review**



# QbR Background (Continued)

- **General framework for a science and risk-based assessment of product quality.**
- **Recommended submission format (see the draft ANDA Submission - Content and Format guidance**
- **Fully implemented for ANDAs in 2007.**
- **Revised chemistry questions in 2012 and 2014 - capture quality-by-design (QbD) approaches**
- **There are multiple benefits realized by using a QbR approach**



# QbR Format

- **Series of focused questions divided into three broad categories:**
  - (1) drug substance quality standards,
  - (2) drug product quality standards, and
  - (3) process understanding and proposed drug manufacturing scale-up plans
- **Follows the CTD format**
- **Not intended to replace the detailed supportive information in 3.2 Body of Data**
- **Companion documents are available**
  - Clarify the information that should be provided by applicants in QbR submissions



# **What is the Future of Regulatory Submissions?**



# CMC Regulatory Submissions – The future is now!

- **Functional**
  - **Electronic**
  - **Structured**
  - **Searchable**
- **Flexible**
  - **Dosage-form specific**
  - **Facilitate OPQ Team Quality Assessment**
- **High Quality**
- **Level of detail**
- **Clarity - Control Strategy / Established Conditions**



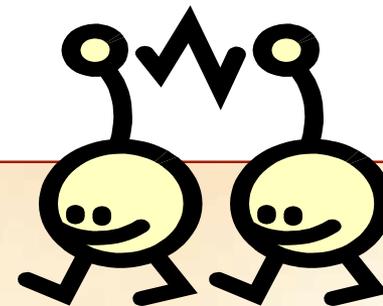
# CMC Regulatory Submissions – The future is now!

- **Lifecycle**
  - Submission, Product, Sites
  - Delineation of Established Conditions
- **Risk & Science Based**
- **Knowledge Management**
  - Not just data...
  - Cohesive
  - Comprehensive & Concise ?
  - Experience and Prior Knowledge Sharing
  - Gain Knowledge - Update Risks, Controls, etc.





# Sharing The Load...



- FDA can...
  - Provide **Transparency & Clear Expectations**
    - Template
    - Guidance
    - Workshops
- Industry can...
  - Provide **High Quality** Submissions
  - Provide **Feedback** / Lessons Learned
  - Openness to “try something new”

**How is QbR a step in the right direction?**



# How is QbR a step in the right direction?

- **Clear Communication**
- **Use of Similar Language**
- **Common Quality Standards**
  - Consistent with the **QbD** paradigm
  - Congruent with **risk management** approaches
  - Encourages **justification** for choices made throughout the development and manufacture
  - Increases **transparency** in the applicant's thought processes



# QbR: *Benefits to Reviewers*

- **Team Based Integrated Quality Assessment**
- **Make Better Risk Based Decisions**
- **Effective Quality Assessment**
  - **Guides reviewers** for consistent and comprehensive quality evaluation
  - Includes **level of risk** associated with design and manufacture of the product
  - Provides **consistency** among the submissions
  - Leads to more focused and **efficient** review



# QbR: *Benefits to Applicants*

- **Clear Communication**
- **Effective Quality Assessment**
- **Common Quality Standards**
  - **Standardizes** submission expectations
  - Provides **clear expectations**
  - Provides an opportunity to address **critical questions** about the product's design, failure risk, and manufacturing controls from both a performance and patient usability perspective.
  - **Reduces questions** from the reviewers during the review cycles
  - Use as an internal **communication tool** (e.g., reg. affairs with development, etc.)

# **Trying QbR Approaches for NDA Review**



# QbR for New Drug Applications (NDA)

- **Explored utilization of QbR approach for NDA review:**
  - **Support adoption of a science and risk based review**
  - **Standardize review approach for both NDA and ANDA**
  - **Facilitate consistent communication with all quality stakeholders**
- **Develop a QbR based review template for both NDA and ANDA**
  - **Supports implementation of integrated team based review within OPQ (Office of Pharmaceutical Quality)**



# Feasibility of QbR for NDAs

- **Initial Steps – OPS/Q TAG (Technical Advisory Group) team set up**
  - **Included expert QbR users from Generic Drug Chemistry and review staff from ONDQA (Office of New Drug Quality Assessment) to explore feasibility of implementation of QbR for NDA review**
  - **Develop one set of overarching QbR questions that apply to both new and generic drug products**



# Lessons Learned: QbR Review of NDAs

- Led to a more **focused**, faster review
- Proved useful as a **standardized** review tool
- Enhanced **consistency**
- Differentiated the applicant's response from the reviewer's evaluation
- Use of QbR questions that included risk assessment, QTPP, CQAs, critical properties of intermediates etc. contributed to:
  - Enhanced product and process understanding
  - Facilitated patient centric risk based evaluation
- Challenges to reviewer - the NDA applications did not use the QbR format



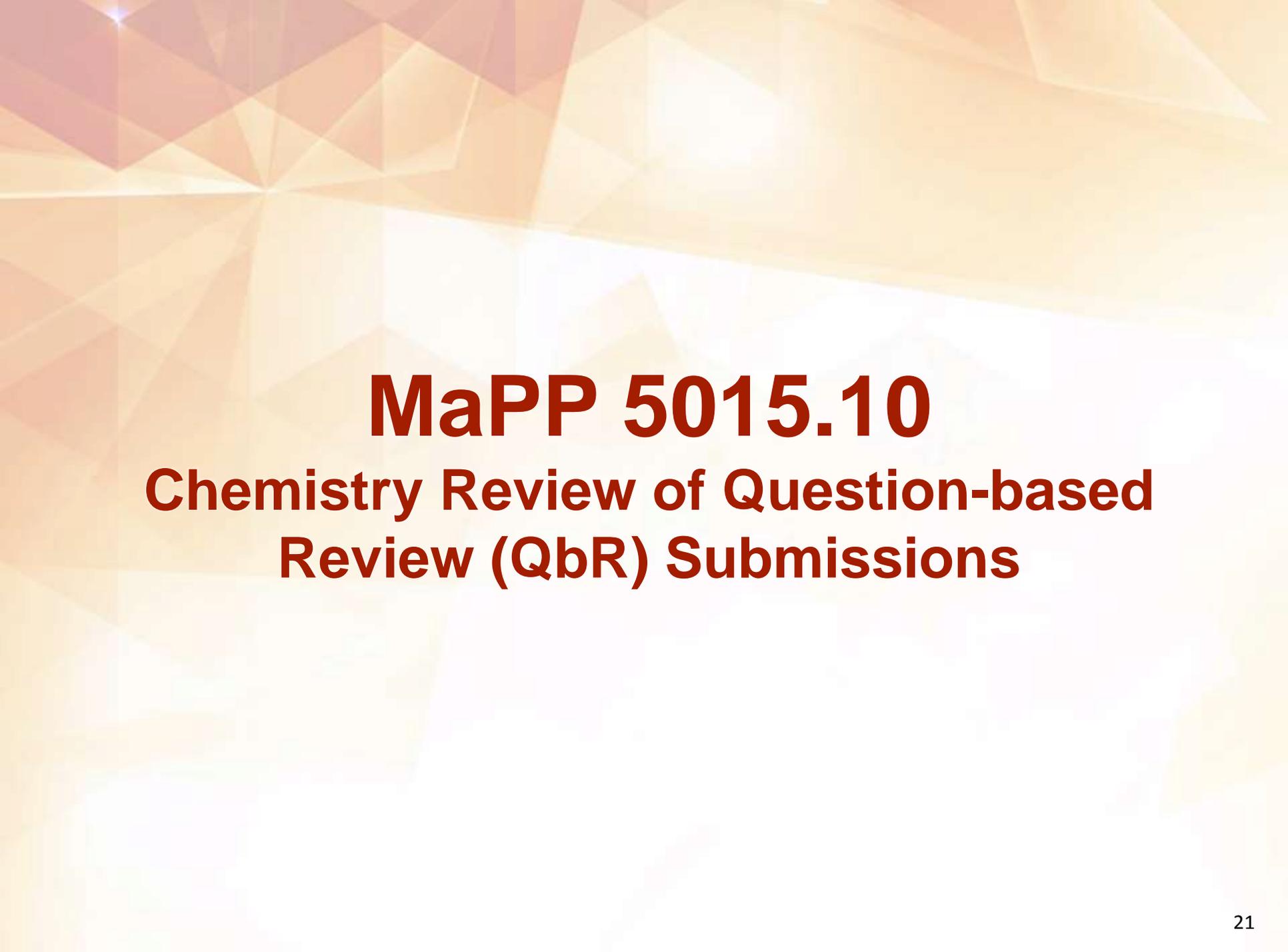
# Lessons Learned: QbR Review of NDAs

- Developed a **single set** of high level questions that address the critical development aspects across various dosage forms & applicable for new and generic drug substance and drug products
- Additional review tools developed:
  - A “Quality Checklist” – “flag” high risk or noteworthy aspects of an application
  - QbR Companion Documents - Contains additional details for each QbR question, e.g.,
    - What the applicant should provide for each question
    - Points of Consideration for Reviewers



# QbR – NEXT STEPS

- **Utilize Lessons Learned from CVM QbR Submission and Review Templates**
- **Look into dosage form or unit operation specific considerations**
- **Revise Internal Procedures and Training Guides (e.g., MaPP 5015.10)**
- **Gather data from use of QbR for integrated quality assessment in OPQ**
- **Continue dialog with external stakeholders (e.g., PhRMA, GPhA, etc.) and other regulatory agencies (e.g. EMA, PMDA, etc.)**



# **MaPP 5015.10**

## **Chemistry Review of Question-based Review (QbR) Submissions**



# MaPP Overview

- Published 11/19/2014
- MAPP clarifies how chemistry reviewers should assess submissions (DMF, ANDA, NDA) that follow a Question-based Review (QbR) format
- MAPP may also be used as a guide for the assessment of submissions that do not follow the QbR format
- Includes reviewer guides and chemistry questions developed by the QbR TAG Team
- Intended to “formalize” existing (and new) QbR review process



# MaPP Policy

- Reviewers will use QbR review templates when evaluating applications and DMFs submitted **using a QbR format.**
- Reviewers may still communicate additional questions (via the appropriate route: information request, complete response, easily correctable deficiency, etc.)
- Review divisions may choose to use a QbR review template for applications that are not submitted in the QbR format



# Responsibilities & Procedures

- **Reviewers will:**
  - **Assess submissions using current QbR review template**
  - **Include a summary, if QbR questions are not provided**
  - **Use the QbR companion documents**



# Drug Substance Reviewer Guide (Example)

**6. What is (are) the starting material(s) for the manufacturing process and how would changes in starting material quality and/or synthesis/source be controlled to minimize adverse effects on the drug substance quality?**

***Note to Reviewer: The following information may be considered in response to this question:***

The proposed starting materials should be clearly identified with appropriate specifications. Justification for designation of each starting material should be in agreement with the general principle outlined in ICH Q11. This can include information, if applicable, on:

- Name, address and contact information of the manufacturer(s) of each proposed starting material
- A flow diagram and description outlining the synthetic route and conditions of each proposed starting materials
- Discussion on the impurities (including residual solvents and inorganic impurities), arising from the manufacturing process of each proposed starting material
- The ability of analytical procedures to detect impurities in the starting material
- The fate and purge of those impurities and their derivatives in subsequent processing steps
- How the proposed specification for each starting material will contribute to the control strategy



# Drug Product Reviewer Guide (Example)

## 2.3.P DRUG PRODUCT

### 2.3.P.1 Description and Composition of the Drug Product

**1. What is the description of the proposed commercial drug product? What are the components and composition of the final drug product as packaged and administered on both a per unit dose and %w/w basis? What is the function(s) of each excipient?**

***Note to Reviewer: The following information may be considered in response to this question:***

- Descriptive information of drug product including weight, dimensions, shape, color, em/debossing, score, color of solution, clarity, etc.
- Description of any co-packaged components (e.g., device components).
- Supporting photos of drug product (all strengths) with scale indicated, including a comparison of the generic to RLD when applicable should be provided. A link to Module 3 may be used.



## Responsibilities & Procedures (cont.)

- ***Drug Substance & Drug Product Reviewers will:***
  - **Read and consider all relevant information submitted by the applicant (e.g., QOS and body-of-data sections) while preparing the primary review; and be mindful that information submitted in the QOS (Module 2) should not contradict information provided in the body of data (Module 3)**



# References/Resources

- **MaPP 5015.10**

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM423752.pdf>

- **ICH M4Q: The CTD - Quality**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf>



# References/Resources

- **QbR Questions for Terminally Sterilized & Aseptically Filtered Products**

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm319925.htm>

- **ANDA Labeling QbR Questions**

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm321987.htm>

- **Guidance for Industry (DRAFT) ANDA Submissions - Content and Format of Abbreviated New Drug Applications**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf>

# **Frequently Asked Questions on MaPP 5015.10**



# FAQ

## Question #1:

**Does an applicant need to submit the CMC QbR against to the latest questions listed under MAPP 5015.10?**

## Response #1:

**Applicants may use the questions found in MaPP 5015.10, at this time the 2007 QbR questions may still be used.**



# FAQ

## Question #2:

**Is there any expected implementation time period from FDA for QbR questions listed in MAPP 5015.10?**

## Response #2:

**FDA plans to finalize the revised QbR questions in parallel with the draft ANDA Content and Format Guidance for Industry.**



# FAQ

## Question #3:

- **Is it acceptable for an applicant to reference a DMF for information not be included in the “open part” of DMF supplied to an ANDA applicant?**

## Response #3 (Part One):

- **MaPP 5015.10 was developed for assessment of ANDAs, NDAs and DMFs that are submitted using a QbR format.**
- **The industry (including DMF holders) may use the information found in the MaPP as a guide to formatting their submissions.**



# FAQ

## Response #3 (Continued):

- The intent of this MaPP is not to require proprietary or restricted DMF information to be submitted in an ANDA or NDA.
- You may reference an authorized DMF in your submission for any proprietary or restricted information.
- An **applicant is still responsible** for providing drug substance information, as required by current regulations and as recommended in current guidance, including drug substance quality attributes that link to drug product quality attributes.



# FAQ

## Question #4:

- Please clarify that in the case of a significant change during the accelerated stability studies, whether 12 months (per the MAPP) or 6 months (per the ANDA stability guidance) intermediate data required at the time of submission for ANDA acceptance?

## Response #4:

- **This MaPP is not intended to change current recommendations** in the relevant stability guidance documents noted above.
- An ANDA applicant should still submit 6 months of long-term and accelerated data at the time of submission. If there is a significant change observed in the accelerated data, the applicant should submit 6 months of intermediate stability data at the time of submission.
- These data should be updated with data during the review cycle as noted in the ANDAs: **Stability Testing of Drug Substances and Products - Questions and Answers** guidance.



# **Beyond QbR...**

## ***The Future of Regulatory Submissions***

- **How to “package” the development history and control strategy?**
  - **What is the control strategy, what are the “established conditions” or “regulatory commitments”?**
  - **Linking a “Post-Approval Change Management Plan”**
- **How can we better present knowledge gained (not just data available) in Annual Reports and Supplements over product and submission Lifecycle?**
- **How best to communicate risks for overall Quality Assessment (API/DP/Mfg./Site)?**



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## **Thank you for your attention!**

### **OPQ Questions?**

[CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov)

Session Evaluation:

[surveymonkey.com/s/GDF-D2S4](https://surveymonkey.com/s/GDF-D2S4)